REMARKS

This is responsive to the Office Action of 21 March 2003.

Support for Amendments to the Specification

The Applicant has amended typographical errors in paragraphs 8, 17, 20, 31, 43, 46 and 56, and in Example 1 on page 17 of the Specification. The Applicant has also amended paragraph 21 by adding the sentence "Preferably, the temperature is between 240-300°C and the pressure is between 3.5~8.4 MPa." The Applicant submits that support for this amendment is found in Examples 1 and 2 on pages 17 and 18, where it is disclosed that the compounds PAM-120 and PBM-100, which are completely free of glucosyl groups, and PAN-20, which only has one glucosyl group at position 3, are produced by exposing ginseng extract to a temperature of 240°C and 3.5 MPa (shown in Example 1) or 270°C at 4.5 MPa (shown in Example 2). The Applicant submits that no new matter has been added by this amendment.

Support for Amendments to the Claims

The Applicant has amended claim 1 by deleting portions of the claim directed to the compounds PBM-110, PAN-20 and PAN-30. The Applicant has also cancelled claims 4, 5, 6, 11, 12, and 13, which were directed to these compounds.

The Applicant has also cancelled claims 7, 8, 15, and 17 to 24.

The Applicant has added claims 34 to 37 which are directed to embodiments of the sapogenins PAM-120 and PBM-100 as claimed in claim 1. These embodiments were formerly the subject matter of claims 19 to 22. Claim 33 has also been added to claim the sapogenins as claimed in claim 1 wherein the sapogenins are incorporated into a food, a health food, a nutritional product, a natural product, or an alternative medicine product. The Applicant submits that support for this claim is found in paragraph 19 on page 6 of the Specification.

Claims 38 to 40 have been added to claim a method of treating lung cancer cells using PAM-120 and PBM-100. The Applicant submits that support for these claims is found in Example 3 on pages 18 to 20, including Table 2.

Claims 41 to 43 have been added to claim a method of treating sarcoma tumor cells using PAM-120 and PBM-100. The Applicant submits that support for these claims is found in Example 4 on pages 20 and 21, including Table 3.

Claim 44 has been added to claim a method of prolonging the life span of a patient suffering from sarcoma. The Applicant submits that support for this claim is found in Example 5 on pages 22 to 23, including Table 4.

Claims 45 to 47 have been added to claim a method of treating melanoma cells using PAM-120 and PBM-100. The Applicant submits that support for these claims is found on page 23, paragraph 55 and in Figure 1.

Claims 48 to 55 have been added to claim a method for treating breast cancer cells using PAM-120 and PBM-100. The Applicant submits that support for these claims is found on pages 23 and 24, in paragraphs 56, 57, and 58, and in Figure 2, Figure 3, and Figure 4.

Claim 56 has been added to claim a method of treating malignant glioma cells using PAM-120. The Applicant submits that support for this claim is found on pages 24 and 25, in paragraphs 59 and 60, and in Figure 6.

Claims 57 to 68 have been added to claim specific dosages for the sapogenins used in the methods for treating various cancers as claimed in claims 38, 41, 44, 45, 48, and 56. The Applicant submits that these dosages had been previously claimed in claims 17 and 18, which have now been cancelled. The dosages are also referred to in the Specification on page 6 in paragraph 17.

35 USC § 112 Rejection of Claims 7, 8, and 14-24

The Examiner contends that claims 7, 8, and 14 to 24 contain subject matter which was not described in the Specification in such a manner as to enable one skilled in the art to make or use the invention. The Examiner contends, on page 3, that the invention is directed to dammarane saponins and sapogenins and their method of use for the "treatment of cancer," and that "no compound has ever been found that can treat cancers generally even though massive efforts have been directed towards this end. Nearly all anticancer drugs are effective against only a limited group of related cancers." The Examiner contends that since the nature of methods of cancer treatment are unpredictable, and since the claims are drawn to a broad range of pharmaceuticals, and since there is a lack of guidance in the

Specification, a person skilled in the art would have to undertake undue experimentation to practice the claimed invention.

The Applicant has cancelled claims 7, 8, 15 which were directed to methods of treating cancer by administering the compounds of the invention. The Applicant has added claims 38 to 56, which are directed to the treatment of **specific** cancer types using the sapogenins PAM-120 and PBM-100. As discussed above, the Applicant submits that support for these claims is found in Examples 3 to 5, and in Figures 1 to 6.

The Applicant has amended claims 14 and 16 so that they are directed to a method of treating cancer comprising administering one or more of the sapogenins as claimed in claim 1. The Applicant submits that the Specification would enable a person skilled in the art to practice the invention claimed in claims 14 and 16, as amended.

Claims 14 and 16 are limited to the use of the sapogenins as claimed in claim 1, namely PAM-120 and PBM-100, in methods of treating cancer. Because the claims are only directed to two chemicals, the claims are **not** claiming a "broad range of pharmaceuticals" as the Examiner has alleged. Furthermore, the Applicant submits that the specification is still considered to be enabling even if a reasonable amount of **routine experimentation** is required in order to practice the claimed invention (*In re Wands*, 858 F.2d at 736-37, Fed.Cir.). Therefore, if any experimentation is necessary to practice the invention, the Applicant submits that the experimentation would only be routine experimentation. The Examiner contends that "there is no drug which is broadly effective against all forms of cancer," citing a reference from Chemotherapy of Cancer, published in 1981. The Applicant submits that since 1981, numerous advances have been made in cancer research and the date for determining whether a specification is enabling is the **filing date of application** (*Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed.Cir. 1986). The Examiner has also stated on page 4 of the Office Action that "[a] disclosure should contain **representative examples**, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. The Applicant submits that it has demonstrated in Examples 3 to 5, and in Figures 1 to 6 that sapogenins PAM-120 and PBM-100 are **effective against various different types of cancer cells**, including lung cancer cells, sarcoma tumor cells, melanoma cells, breast cancer cells, and malignant glioma cells. The Applicant submits that it has also demonstrated that the sapogenins are effective when used in combination with other anti-cancer treatments, such as taxol and cisplatin. In light of the fact that the Applicant has demonstrated the effectiveness of PAM-120 and PBM-100 against multiple types of cancer

cells, the Applicant submits that the Specification enables a person skilled in the art to practice the invention as claimed in claims 14 and 16.

35 USC § 102 Rejection of Claims 1, 4, 11, and 13

The Applicant has deleted portions of claim 1 directed to compounds PBM-110, PAN-20, and PAN-30, and the Applicant has cancelled claims 4, 5, 6, 11, 12, and 13 which were directed to these compounds.

35 USC § 103 Rejection of Claims 1 to 24

The Examiner has maintained the rejection of claims 1 to 24 under 35 USC § 103(a) as being obvious in light of Japanese Abstract No. JP08291194 issued to Hasegawa Hideo et al. ("Hideo") and PCT Publication No. WO 97/31933 filed by Park et al. ("Park"). The Examiner has further rejected claims 1 to 24 as being obvious in light of Jong-Dae Park et al., Arch. Pharm Res. Vol. 19, 213-218 (1996) ("Park et al."), Taik-Koo Yun et al., J. Korean Med. Sci. (2000, 16(Suppl), S6-18)("Yun"), and Sun Won Kwon et al., J. of Chrom. A, 921 (2001), 335-339 ("Kwon"). On page 6 of the Office Action, the Examiner asserts that the cited prior art discloses compounds which differ from the claimed compounds in the position of the double bond in the side chain at position 17. The Examiner has asserted that the compounds claimed in the application are positional isomers of the prior art compounds. Because the prior art teaches the use of dammarane sapogenins or saponins as anticancer and antitumor agents, the Examiner contends on page 7, paragraph 2 of the Office Action, that "even though by disclaiming certain compounds for anticipation, instant invention is considered obvious over the prior art, because instant invention is the positional isomer of the prior art."

The Applicant has cancelled claims 4, 5, 6, 11, 12, and 13 which are directed to the compounds PBM-110, PAN-20 and PAN-30. The Applicant has also amended claim 1 to remove references to compounds PBM-110, PAN-20 and PAN-30. The remaining portion of claim 1, and claims 2, 3, 9, and 10 are directed to the compounds PAM-120 and PBM-100. The Applicant respectfully submits that compounds PAM-120 and PBM-100 are not obvious in light of the prior art and requests withdrawal of the 35 USC § 103 rejection in light of the following.

The Applicant submits that the compound PBM-100 is not a positional isomer of any of the compounds disclosed in the cited prior art. None of the cited prior art compounds contain a hydroxyl group and 2 double bonds in the side chain attached at position 17.

Furthermore, the Applicant submits that PBM-100 is sufficiently different from the cited prior art compounds that a person of ordinary skill in the art would not be motivated to isolate or prepare such a compound having regard to the prior art. As discussed above, PBM-100 is different from the cited prior art compounds because it has an additional hydroxyl group and double bonds in the side chain at position 20. The Applicant submits that hydroxyl groups are known to persons skilled in the art to be reactive groups and that the presence of double bonds results in differences in stereo-chemistry. Therefore, a person skilled in the art would not expect or predict that a compound having additional hydroxyl groups and double bonds would have the same or even similar activity as known compounds that do not have fewer hydroxyl groups and double bonds.

Furthermore, in a telephone conversation with the Applicant's agent, the **Examiner advised that claim 10, which is directed to the compound PBM-100, should not be included in the 35 USC § 103 rejection**, and that the Examiner would withdraw the rejection to claim 10 . Therefore, the Applicant respectfully requests allowance of claim 10 and claims 40, 43, 47, and 51, which are directed to methods of treating various types of cancer using the compound PBM-100.

The Examiner has also rejected claims directed to the compound PAM-120 as the Examiner contends that PAM-120 is a positional isomer of the compound dammara-20(22),24-diene-3β,12β-diol ("Quasi-protopanaxadiol") disclosed in Hideo. Because Hideo discloses that Quasi-protopanaxadiol has anti-cancer properties, the Examiner alleges that in the absence of comparative data to compare the activity of PAM-120 against the activity of Quasi-protopanaxadiol, the claims directed to the compound PAM-120 are considered obvious in light of Hideo.

The Applicant submits that PAM-120 has surprising and unexpected characteristics over Quasi-protopanaxadiol. Attached as Appendix "A" hereto is the affidavit of Dr. William Jia, pursuant to 37 C.F.R. 1.132, which provides comparative data on the activity of PAM-120 and Quasi-protopanaxadiol. The Applicant submits that the data demonstrates that **PAM-120 is considerably and unexpectedly more effective** against the same types of cancer cells that Quasi-protopanaxadiol was tested against in Hideo. PAM-120 also likely

affects the cancer cells through a **different mechanism of action** than Quasi-protopanaxadiol, which also could not be predicted.

The Applicant has repeated the experiments that are disclosed in Hideo, using PAM-120 in place of Quasi-protopanaxadiol, and compared the results using PAM-120 against the results disclosed in Hideo. As shown in Table 2 in the affidavit of Dr. William Jia, PAM-120 is much more effective at sensitizing multiple-drug resistant mouse leukemia cells P388ADM to the chemotherapy agents daunomycin and vinblastine. At a concentration of only 0.5 μM, PAM-120 sensitized the P388ADM cells so that the same concentration of daunomycin was as effective against the multiple-drug resistant cells as against the non-drug resistant P388 cells. At 0.5 μM, PAM-120 was also able to reduce the resistance of P388ADM cells to vinblastine to only 1.43 times the resistance demonstrated by the non-drug resistant cells. At a concentration 1.0 μM, PAM-120 sensitized the P388ADM cells to daunomycin and vinblastine even more.

However, according to the data disclosed in Hideo, at a concentration of **37.5 μM**, Quasi-protopanaxadiol was not able to sensitize the P388ADM cells as well as PAM-120 at a concentration of only **1 μM.** Therefore, at a considerably lower concentration (i.e. 1/37.5 of the concentration required of Quasi-protopanaxadiol), PAM-120 more effectively sensitized the cells. Therefore, PAM-120 has unexpected and superior characteristics over Quasi-protopanaxadiol.

Furthermore, as shown in Table 1 of Dr. Jia's affidavit, the IC50 of PAM-120 against P388ADM cells is **9.58 μM.** In Hideo, the IC50 of Quasi-protopanaxadiol is **45.3 μM** (it is not disclosed which cell line this IC50 was determined for, therefore, the Applicant has assumed that it is the P388ADM cell line). Therefore, the IC50 of PAM-120 is **at least less than 1/4** of the IC50 of Quasi-protpanaxadiol.

Moreover, as discussed above, at 1 μM, PAM-120 is capable of sensitizing the P388ADM cell line to a greater degree than Quasi-protopanaxadiol at a concentration of 37.5 μM. 1 μM is **less than 1/9th** the IC50 of PAM-120. However, for Quasi-protopanaxadiol, the concentration of 37.5 μM is **83%** of its IC50. Therefore, the Applicant submits that not only is PAM-120 more effective at sensitizing P388ADM cells to anti-cancer drugs, but it likely sensitizes the cells using a **different mechanism of action.** Therefore, the Applicant submits that PAM-120 has surprising and unexpected characteristics which are **not obvious** having regard to Quasi-protopanaxadiol. In light of the foregoing, the Applicant respectfully requests withdrawal of the citation of Hideo from this application.

In light of the foregoing, the Applicant submits that this application in condition for allowance, which is respectfully requested.

Respectfully submitted,

By: 

Peter J. Butch III
Reg. No. 32, 203

Synnestvedt & Lechner LLP
2600 Aramark Tower
1101 Market Street
Philadlephia, PA 19107

Tele: (215) 923-4466
Fax : (215) 923-2189